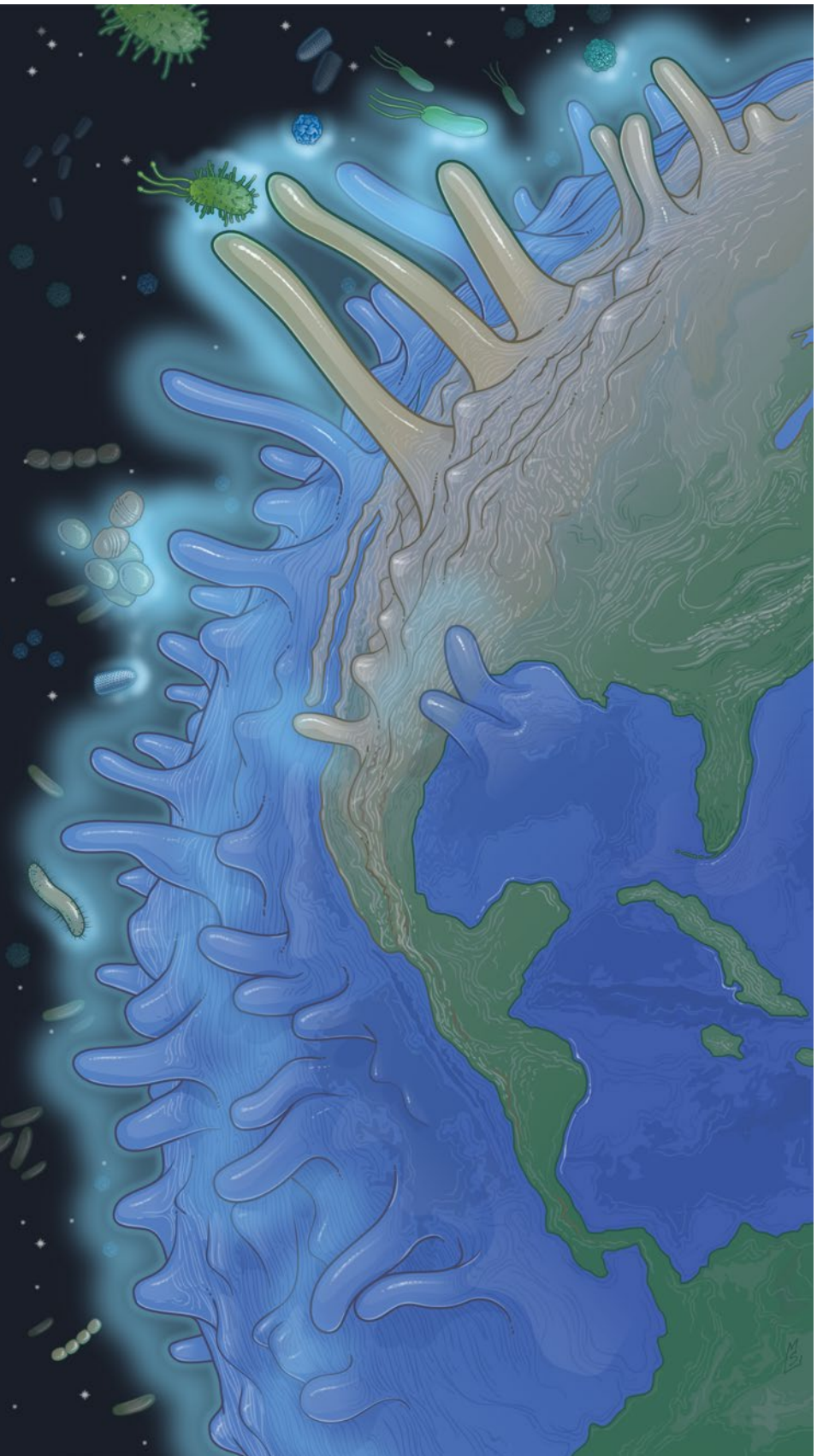


**FASEB**  
Federation of American Societies  
for Experimental Biology



# Breakthroughs in Bioscience

Developed by the Federation of American Societies for Experimental Biology (FASEB) to educate the general public about the benefits of fundamental biomedical research.



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# Acknowledgments

## Vaccines: Essential Weapons in the Fight Against Disease

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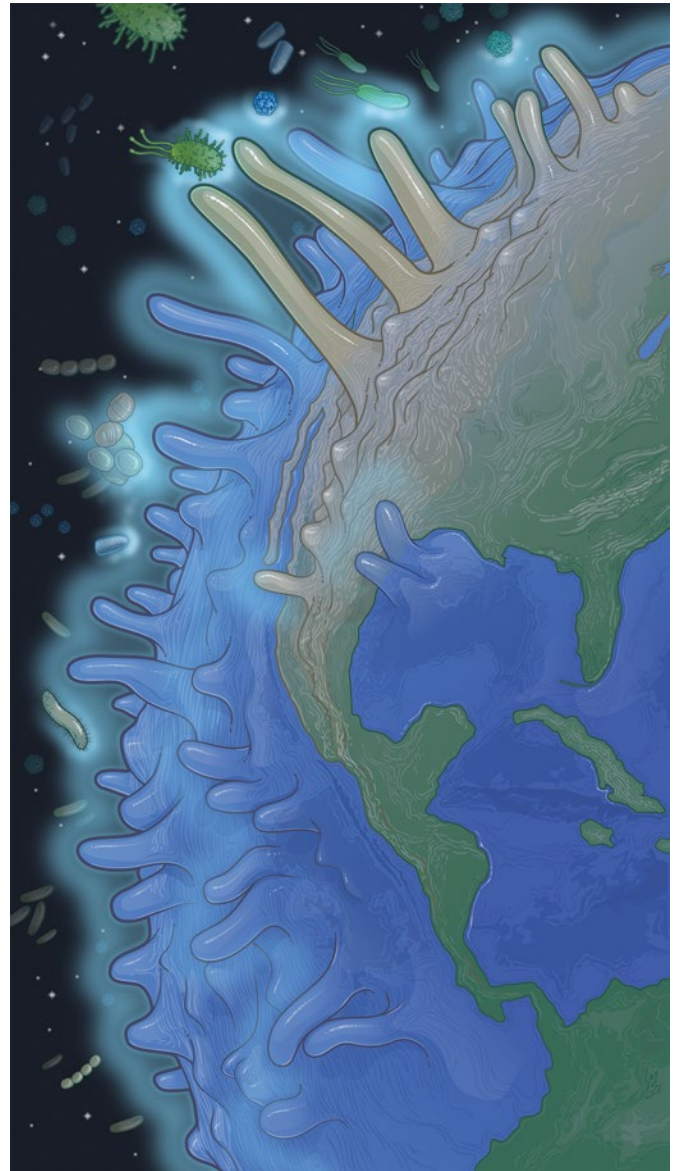
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**COVER:** Vaccines are powerful weapons in the fight against disease. They have averted more than 100 million cases of disease in the United States and continue to prevent 2.5 million deaths globally every year. By answering some very basic questions, such as what enables a guinea pig to defend itself against a toxin, how do starfish and other animals without stomachs process their foods, and what protects fruit flies from fungal infections, researchers laid the foundation for an impressive vaccine armory to fight infectious diseases and cancers.

Cover illustration: © Michael Linkinhoker, Link Studio, LLC



This article was developed in collaboration with The American Association of Immunologists.

# VACCINES: Essential Weapons in the Fight Against Disease

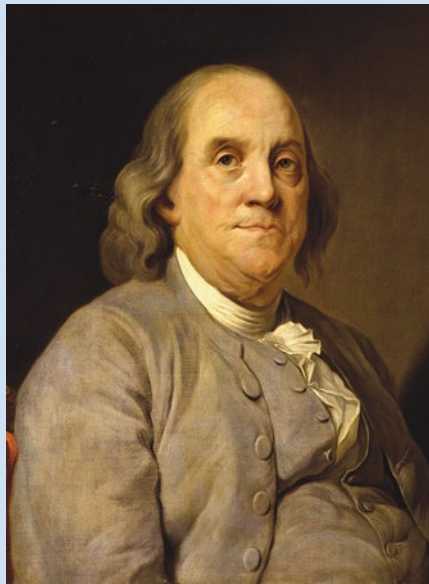
*An ounce of prevention is worth a pound of cure.*

– Benjamin Franklin

Imagine a world in which playgrounds and pools are closed because of polio epidemics, and elementary school playmates are dying from diphtheria or whooping cough, while others are permanently left deaf, blind, or sterile due to measles, mumps, or meningitis. Only a generation or two ago that world was a frightening reality that contributed to one out of five children never reaching adulthood in the United States. Repeated epidemics swept through the world, killing as many as one-quarter of the population, many of whom were healthy and vibrant before an infectious disease led them to their graves.

Fortunately, that world no longer exists because of tremendous progress made in vaccine development and application. There are now more than two dozen vaccines that can prevent death or disability from infectious diseases such as influenza, polio, meningitis, and measles. Vaccines have prevented more than 100 million cases of disease in this country alone and continue to prevent 2.5 million deaths worldwide each year—the equivalent of averting about 7,000 deaths each day. With the exception of safe drinking water, no other single health measure has saved so many lives as vaccines. Vaccines also are highly cost effective. Routine vaccinations administered to US children between 1994 and 2013 are estimated to save \$295 billion in direct health care costs and an additional \$1.3 trillion in indirect costs ranging from missed work to permanent disability.

## BENJAMIN FRANKLIN



*Image credit: Joseph-Siffrein Duplessis (Public domain), via Wikimedia Commons*

Perhaps the most poignant advocate for variolation (inoculation with the live smallpox virus) was Benjamin Franklin. Franklin writes in his autobiography, “I lost one of my sons, a fine boy of four years old, by the small-pox, taken in the common way. I long regretted bitterly, and still regret that I had not given it to him by inoculation. This I mention for the sake of parents who omit that operation, on the supposition that they should never forgive themselves if a child died under it; my example showing that the regret may be the same either way, and that, therefore, the safer should be chosen.”

Although the first vaccines stemmed from observations made centuries ago that survivors of epidemics were naturally immune to the same disease, current vaccine successes come from the efforts of hundreds of researchers over the last century and a half. By pursuing basic research, they uncovered what causes disease, how our immune system fights such illnesses, and ways to harness and enhance our natural ability to combat infection.

Basic research also fuels advances in vaccines and underlies recent breakthroughs, including innovative HIV, malaria, and Ebola vaccines that

are showing promise in clinical tests. In an age when global travel facilitates the rapid spread of deadly epidemics and antibiotic-resistant infections are becoming more and more common, vaccines are increasingly important as powerful weapons against infectious disease.

## The safer should be chosen

It is May of 1796 and, along with the blooms of flowers, a deadly smallpox epidemic is sweeping across England. The disease is called the “speckled monster” because of the disfiguring



**Figure 1 – Portrait of Edward Jenner inoculating boy:** Jenner’s smallpox vaccine slashed the incidence of smallpox in half throughout the world by the time he died in 1823. *Image credit: Wellcome Images/Science Source*

scars it leaves behind. It is killing more than three-quarters of infants, and one-third of its survivors end up blind.

Hearing tales that milkmaids are naturally immune to the disease after suffering a milder cow pox rash, the English country physician Edward Jenner hopes to offer similar natural protection to his patients. He finds a young dairymaid with cowpox blisters and uses a lancet to insert the pus from her blisters under the skin of an eight-year old boy. The boy develops a fever and loses his appetite, but he fully recovers ten days later. That summer Jenner gives the boy a similar inoculation, but this time with pus taken from a fresh smallpox blister. As Jenner expected, the boy stays healthy and is one of the first to be successfully vaccinated for smallpox. Jenner’s vaccine works because, unknown to anyone at the time, the virus that causes smallpox is so closely related to the cowpox virus that the experimental vaccine triggers an immune response offering protection from both. The term vaccination was initially used to describe inoculation against smallpox using the cowpox virus, but the term today signifies inoculation against any disease.

Four years after Jenner’s success, physicians are using the revolutionary smallpox vaccine throughout England and much of Europe, as well as in the nascent US. By the time Jenner dies in 1823, his vaccine has slashed the incidence of smallpox in half throughout the world. By 1979, smallpox is eradicated worldwide, such that smallpox vaccinations are no longer deemed necessary for the general public.

Jenner was unaware that microbes triggered disease and was acting merely on the anecdotal observation that milkmaids were protected from smallpox. Further progress in vaccines wouldn’t come until nearly a century later when researchers began solving an ancient puzzle: what causes infectious diseases and how do our bodies naturally fight them?

## Germ theory and rabies averted

As late as the mid-nineteenth century, infectious disorders were attributed to poisonous vapors, planetary influences, or bad smells. Anton van Leeuwenhoek gleefully reported seeing what he called “living



**Figure 2 – Louis Pasteur supervising rabies inoculation:** Pasteur’s discovery that injections of weakened viruses or bacteria protected people from the disease led to his successful creation of vaccines for rabies and other diseases. *Image credit: National Library of Medicine*

animalcules” under his microscope a century before Jenner began vaccinating. No one made the link between Leeuwenhoek’s microbes and disease, but that changed in the 1870s when an epidemic began killing silkworms. The French chemist Louis Pasteur had previously discovered that certain bacteria spoiled the broth of the fermenting grains and grapes used to make beer and wine. So the silk industry in southern France asked Pasteur if he could also figure out the source of the epidemic in silkworms that was destroying their operations. Pasteur’s microscopic observations of the diseased worms and eggs revealed telltale spores of a parasitic fungus and led him to the correct hypothesis that the disease could be prevented by selecting silkworm eggs not infected by the spores.

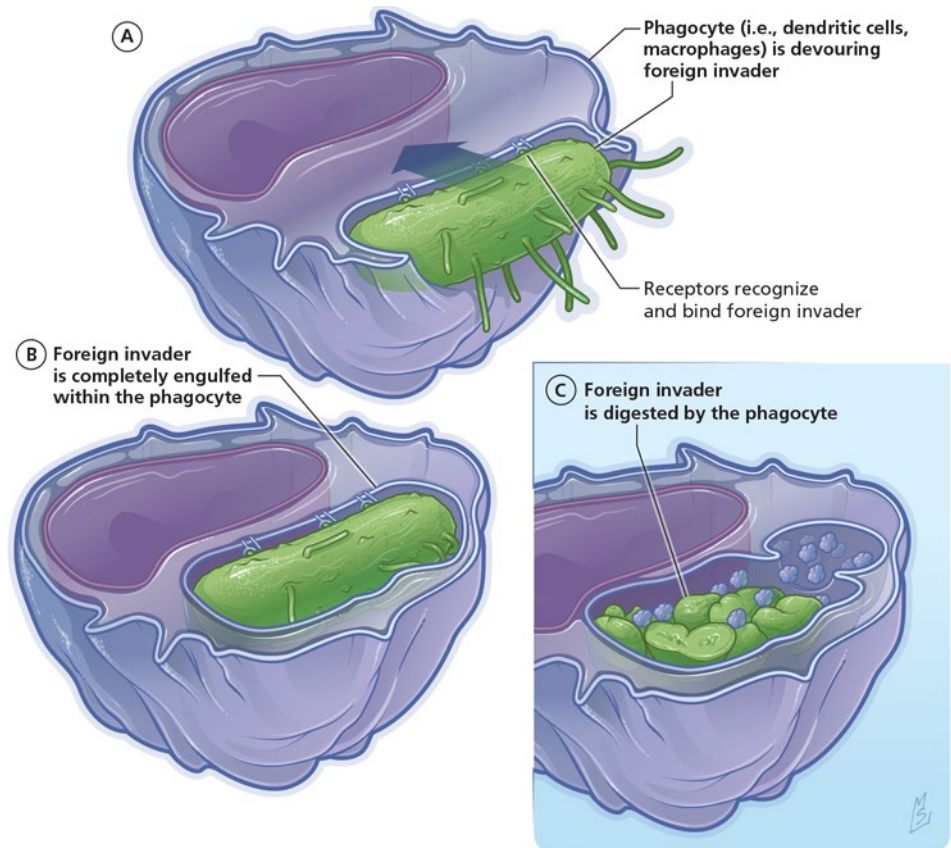
Shortly thereafter, Pasteur proposed his germ theory, which postulated that all infectious diseases were caused by tiny organisms invisible to the naked eye

called germs. The German physician Robert Koch made further refinements to the germ theory, set forth methods to determine whether a particular agent is responsible for disease, and triggered a worldwide hunt for disease-causing germs. Twenty years later, Pasteur, Koch, and other researchers had uncovered the origin of many common deadly diseases, such as leprosy, tuberculosis, cholera, and the plague.

It was while trying to uncover the cause of an epidemic of cholera in chickens that Pasteur made one of the most important discoveries in the history of vaccines. He noticed by chance that old, weakened cultures of the causative bacteria he had isolated from infected chickens lost the capacity to cause major disease in poultry; however, chickens inoculated with the weakened bacteria no longer succumbed to more virulent strains in the wild. He put this basic finding into action in the 1880s, purposely using drying, heating, and other techniques to create weakened strains of microbes.

While working on weakening the virus that causes rabies, he was approached by a physician desperate to save the life of a nine-year-old boy bitten by a rabid dog. Pasteur gave the young lad a dozen injections of weakened rabies virus. The boy survived because the injections triggered his immune system to fight the disease before it took hold in his body. Luckily, rabies, unlike most viruses, has a particularly long incubation period, enabling vaccines to be effective when given soon after exposure to the virus.

Shortly thereafter, researchers created several vaccines by weakening or killing the microbes that cause tuberculosis, typhoid fever, and cholera. Vaccines for diphtheria, tetanus, and whooping cough followed after it was discovered that the toxins produced by their causative microbes could be safely injected after chemical



**Figure 3 – Phagocytosis:** Metchnikoff discovered that cells called phagocytes could engulf microbes and then digest them with enzymes in specialized sacs called phagosomes. This process is called phagocytosis and is a critical weapon of the immune system. *Illustration: © Michael Linkinhoker, Link Studio, LLC.*

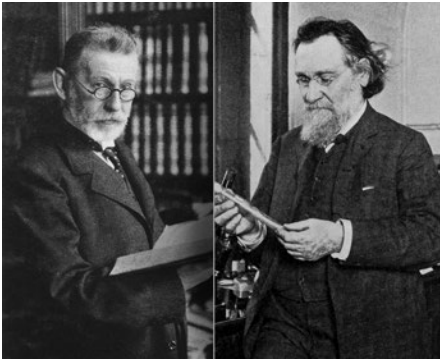
inactivation. These, too, prompted a natural immune response.

## Magic bullets and devouring cells

Further progress in fighting diseases with vaccines awaited a basic understanding of the immune system and how it naturally responds to infections. Fortunately, that got underway by the close of the nineteenth century when the German scientist Emil Behring stunned his colleagues by showing he could protect a guinea pig from deadly diphtheria toxins using a shot of serum gathered from another guinea pig that had recently recovered from the same disease.

This led his colleague, chemist Paul Ehrlich, to postulate that there must be agents in the blood that could

seek out and destroy specific toxins like magic bullets, which prompted Behring to coin the term “anti-body.” Ehrlich imagined that antibodies, with the specificity of a key to a lock, fit around and blocked the action of foreign substances called antigens that circulate in the blood. (See the *Breakthroughs in Bioscience* article, “Magic Bullets and Monoclonals: An Antibody Tale.”) Once a highly specific antibody recognizes and latches on to the antigen it fits, the immune system is stimulated to produce this type of antibody in large numbers to fight infection, Ehrlich postulated. This response came to be known as adaptive immunity. Antigens that provoke an immune response, it was later discovered, were not limited to circulating toxins made by microbes but included the proteins and sugars that protrude from the cell walls or



**Figure 4 – Paul Ehrlich and Elie Metchnikoff:** Ehrlich (left) and Metchnikoff (right) shared the 1908 Nobel Prize in Physiology or Medicine for their discoveries of how the immune system fights infections. Ehrlich’s breakthrough on antibodies and Metchnikoff’s discovery of cells that can devour microbes caused progress in vaccines to blossom. *Image credits: National Library of Medicine (Ehrlich) and Wikipedia Commons (Metchnikoff)*

capsules of microbes. There are also more hidden internal components of microbes that become accessible to antibodies, but only after some of the microscopic invaders have been destroyed and digested by specialized cells discovered by another colleague of Ehrlich’s, the Russian zoologist Elie Metchnikoff.

Metchnikoff was trying to understand how primitive marine worms that lack stomachs digest their food. Spending continuous hours at his microscope and aided by dyes that bind to and thus allow subcellular structures to be visualized, Metchnikoff discovered that specialized cells in the inner cavities of these worms send out finger-like projections that completely engulf and then digest food particles. He called these cells phagocytes and proposed that they were produced by animals to devour foreign invaders, thus “performing a protective role against injurious agents.” This discovery formed the basis of innate immunity. His next experiment transformed him from a zoologist into a pathologist.

He noted, “I fetched a few rose thorns and introduced them under the skin of some beautiful starfish larvae as transparent as water. I was too excited to sleep that night in the expectation of the result of my experiment.” That result was that hordes of phagocytes had migrated toward the thorns and were gobbling them up.

Metchnikoff’s discovery of phagocytes and the rapid innate immune response was another powerful arm to immune defenses, in addition to the slower, antibody-dependent adaptive response described by Ehrlich. The two men shared the Nobel Prize in 1908 for their basic research that provided the foundation for immunology and triggered a rancorous debate at the time about which arm was most important for immune defenses. This debate wasn’t fully settled until a century later with other Nobel-prize winning discoveries that dramatically changed the pace of vaccine research. But before then, researchers had to meet a few other challenges to make progress in vaccine development, including understanding how viruses like polio cause disease, learning how to grow viruses in large quantities, and making vaccines against bacteria more effective in small children.

## In pursuit of polio

The same year Ehrlich and Metchnikoff won the Nobel Prize, Viennese scientists Karl Landsteiner and Erwin Popper discovered the virus that caused polio, an infectious disease that in severe cases can result in paralysis or death. Progress in developing a vaccine for polio was delayed by the mistaken assumption that the virus entered the body via the nasal passages where it infected nerves that carried it into the brain and spinal cord.

Haunted by images of children encased in breathing machines, called iron lungs, and hoping to learn more from those with mild polio, Dorothy Horstmann and her colleagues at Yale



**Figure 5 – Dorothy Horstmann and Isabel Morgan:** Two women contributed significantly to the development of a successful polio vaccine. Yale University researcher Dorothy Horstmann (left) showed how polio is transmitted, and Isabel Morgan (right) of Johns Hopkins University revealed that inoculation with killed polio virus protected monkeys from the disease. *Image credits: Yale University, Harvey Cushing/John Hay Whitney Medical Library (Horstmann) and The Alan Mason Chesney Medical Archives of The Johns Hopkins Medical Institutions (Morgan)*

University collected blood, nasal, and oral samples from people with the disease in the 1940s. The research on these samples and Horstmann’s further experiments on chimpanzees revealed a surprise finding—poliovirus was transmitted not nasally but orally and traveled briefly in the blood before entering the central nervous system. This led Johns Hopkins University bacteriologist Isabel Morgan to show in 1949 that a killed poliovirus vaccine protected monkeys from the disease.

The same year, John Enders, Thomas Wellner, and Frederick Robbins reported a new technique for culturing large quantities of poliovirus in animal tissues. This was a big advance because researchers needed such an abundant supply of poliovirus to develop and test vaccines for it. Unlike bacteria, viruses had been notoriously difficult to grow in the lab. Building on Morgan’s findings and the new tissue culturing technique, Jonas



**Figure 6 – Polio ward:** Because polio caused paralysis of breathing muscles, many children with the disease had to spend time in the breathing machines depicted here. *Image credit: New York Public Library/Science Source*

Salk of the University of Pittsburgh developed the first successful polio vaccine in 1955. This vaccine led to a tenfold decrease in the incidence of the disease and was followed by an even more effective oral vaccine developed by Albert Sabin that used a weakened form of the poliovirus. Horstmann, Morgan, Salk, and Sabin all received research support from a private foundation created by President Franklin Delano Roosevelt called the National Foundation for Infantile Paralysis, later renamed March of Dimes.

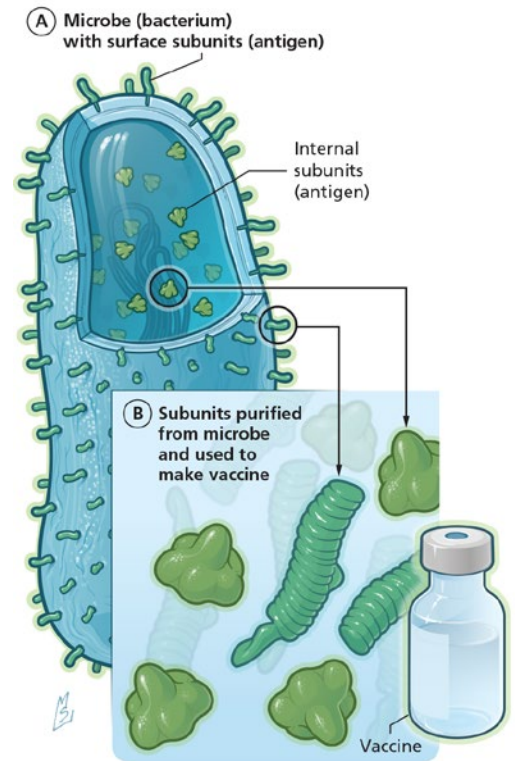
Thanks to both the Salk and Sabin polio vaccines, the world is now on the verge of eradicating polio as it eradicated smallpox years ago. Since 1988, polio infections have decreased by 99 percent, and more than five million people have been saved from paralysis. Polio vaccines were soon followed in the 1960s by vaccines for measles, mumps, and rubella, and more recently by a vaccine for chickenpox. These were enabled

by the pioneering cell culturing techniques for which Enders, Weller, and Robbins won the 1954 Nobel Prize in Physiology or Medicine.

## Subunit and conjugate vaccines

Armed with a basic understanding of how the body naturally defends itself against microbial invaders, researchers began to fine-tune vaccines and experiment to see how little foreign material was needed to elicit an effective immune response. Instead of whole, weakened, or killed microbes, only small portions (subunits) of microbes were used in their vaccines. The goal was to make subunit vaccines comprised of these key portions that could adequately protect against disease but with a minimum of troublesome side effects, such as fever and discomfort at the injection site.

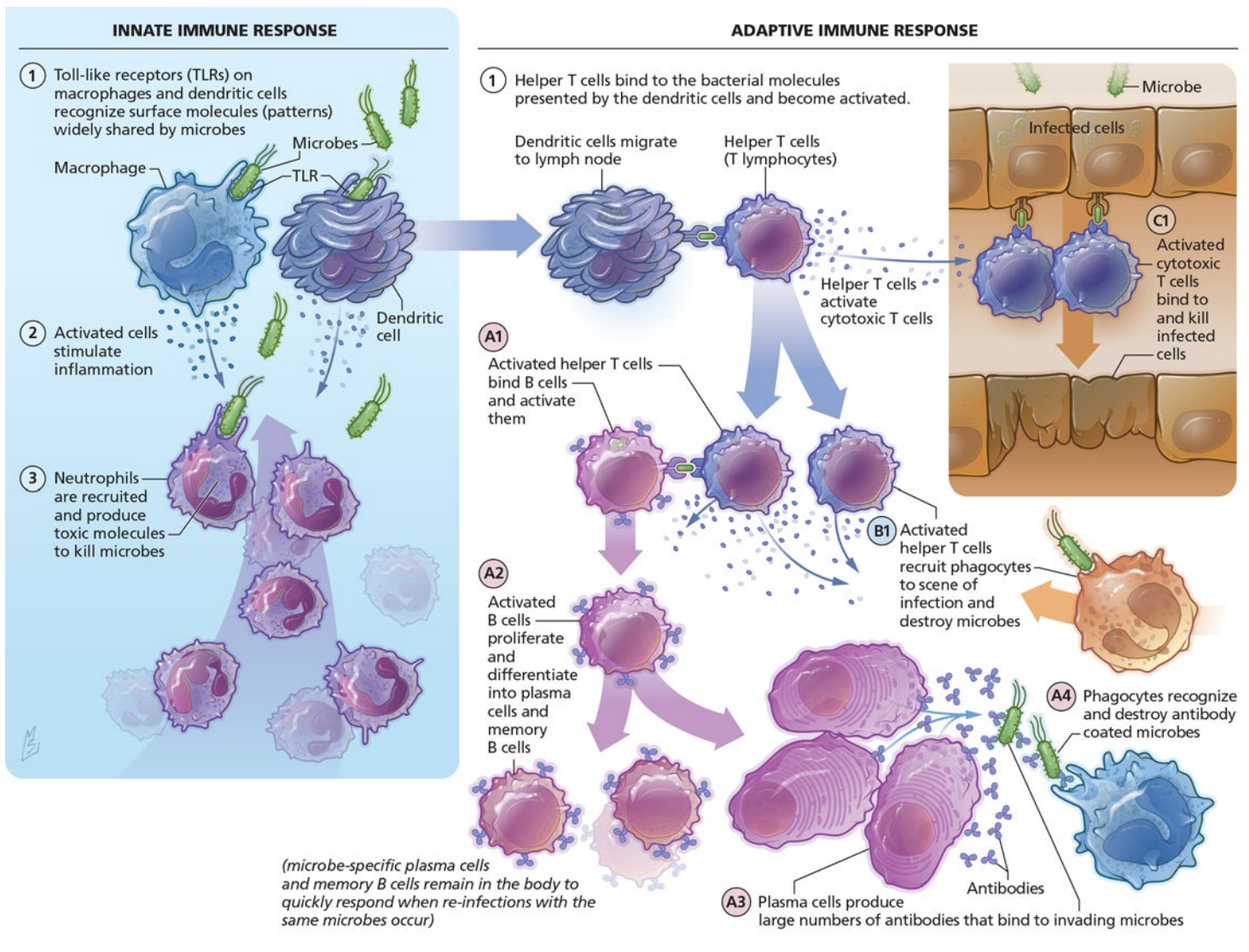
The first subunit vaccine was developed for the pneumococcus bacteria responsible for pneumonia,



**Figure 7 – Subunit vaccine:** Instead of using an entire microbe in its formulation, subunit vaccines only contain the parts from inside or outside of the microbe thought to trigger an effective immune response. *Illustration: © Michael Linkinhoker, Link Studio, LLC*

sepsis (bloodstream infection), and meningitis and came on the market in 1946. Meningitis is a serious infection of the brain and spinal cord most common in young children and causes death in 10 to 15 percent of those who are infected. Many survivors are left disabled due to permanent neurologic damage caused by the infection. Globally, pneumonia kills nearly one million children less than five years of age each year, and in the US, about one million people are hospitalized with pneumonia annually.

Pneumococcus bacteria have an outer coating of sugar molecules that stimulate production of antibodies in animals. Researchers created several subunit vaccines for meningitis and pneumonia using different combinations of these sugars. The



**Figure 8 – Overview of Immune Response:** When a pathogen enters the body, Toll-like receptors on dendritic and other cells recognize surface molecules (patterns) widely shared by microbes (1- Innate Immune Response). These “first responder” cells then display the intruder’s antigens to the helper T cells (1 – Adaptive Immune Response). Helper T cells orchestrate the immune response by activating B cells (A1). Activated B cells develop into memory B cells, sentries that stick around after an initial response to prevent reinfection by the same pathogen (A2), or plasma cells, cells that produce large numbers of antibodies that bind to invading microbes (A3). Antibody coated microbes are subsequently destroyed by phagocytes (A4). Helper T cells can also activate cytotoxic T cells, which detect infected cells and kill them (C1). *Illustration: © Michael Linkinhoker, Link Studio, LLC*

vaccines, however, protected older children and adults from the diseases but not infants and small children who needed the protection most.

*Why?*

The answer to that question came from the serendipitous findings of a young medical researcher working at the National Institutes of Health (NIH) in the 1960s. Prior to that time, scientists knew that blood contained cells called lymphocytes, but what exactly these

cells did was unknown. That changed when Jacques Miller was trying to understand how a virus caused leukemia in mice. It was thought that the virus infected the thymus, a small organ located near the heart that many deemed unnecessary. Miller removed the thymus from newborn mice expecting it would make them immune to the virus and prevent leukemia. Instead, he accidentally discovered that absence of the thymus made the animals more susceptible to all types

of infectious diseases because they lacked a key subset of lymphocytes.

Miller and others went on to show that although they look identical, there are two major types of lymphocytes: B cells and T cells. Both types of cells originate in the bone marrow, but B cells mature in the bone marrow while T cells mature in the thymus. The job of the B cell is to produce antibodies, and T cells are essential conductors of an immune response. Some T cells, called T helper cells, commander

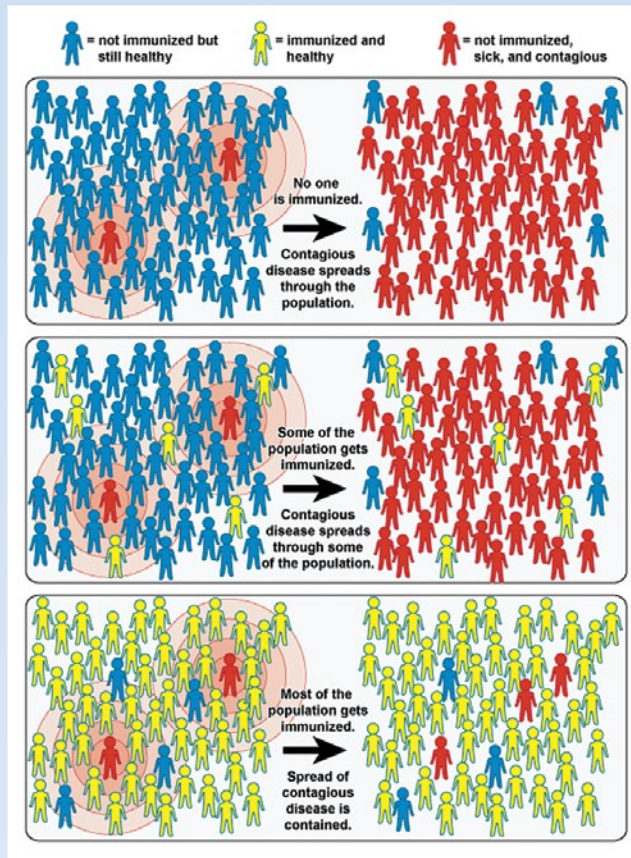


## VACCINE SAFETY

By the time the Food and Drug Administration (FDA) approves vaccines for the market, most have undergone clinical tests on thousands of people, including children. These tests require reporting any serious side effects to the agency. Once vaccines are in widespread use, there is continued surveillance for any side effects that may be linked to them, with reporting of such effects to the Vaccine Adverse Events Reporting System jointly maintained by the FDA and the Centers for Disease Control and Prevention (CDC). The CDC also has other extensive databases from a collaboration of large managed care agencies that it can use to quickly detect and explore possible adverse reactions to vaccines. One such database is called the Vaccine Safety Datalink.

In extremely rare cases, the registry and databases may reveal serious side effects such that the FDA will require a vaccine to be taken off the market. For example, a vaccine for rotavirus, an organism that can cause life-threatening diarrhea in small children, was immediately taken off the market in 1999 when an analysis of reports to the registry revealed that about one out of 100,000 doses of the vaccine was linked to the development of intestinal blockages—a side effect too infrequent to be detected in tests of the vaccine before it entered the market.

Many children will experience some *minor* vaccine side effects, such as fever and discomfort at the injection site. But the risks of *serious* side effects are extremely small and pale in comparison to the risks of the disease itself. For example, the risk of a brain infection (encephalitis) with the measles vaccine is one in three *million*, but the risk of encephalitis from a measles infection is one in one *thousand*. Some proposed side effects of vaccines, such as autism, have no credible data to support them. Unfortunately, misinformation came



**Figure 9 – Herd immunity diagram**

*Image credit: National Institute of Allergy and Infectious Diseases, NIH*

from a fraudulent and unethical study that was later retracted.

With so many vaccines now recommended for small children, some parents worry about overwhelming their babies' immune systems and try to delay certain vaccines to lessen the load at one time. Yet studies show vaccines are as safe when used in combination as used singly, and the thousands of germs a baby's immune system is bombarded with on a daily basis is considerably more than what he or she will ever get from recommended vaccine schedules.

It is more worrisome that vaccines may become a victim of their own success, as parents forget the dreaded diseases for which they offer protection and opt not to vaccinate their children. There are problematic new trends in this regard, including recent outbreaks of whooping cough and measles in children. These

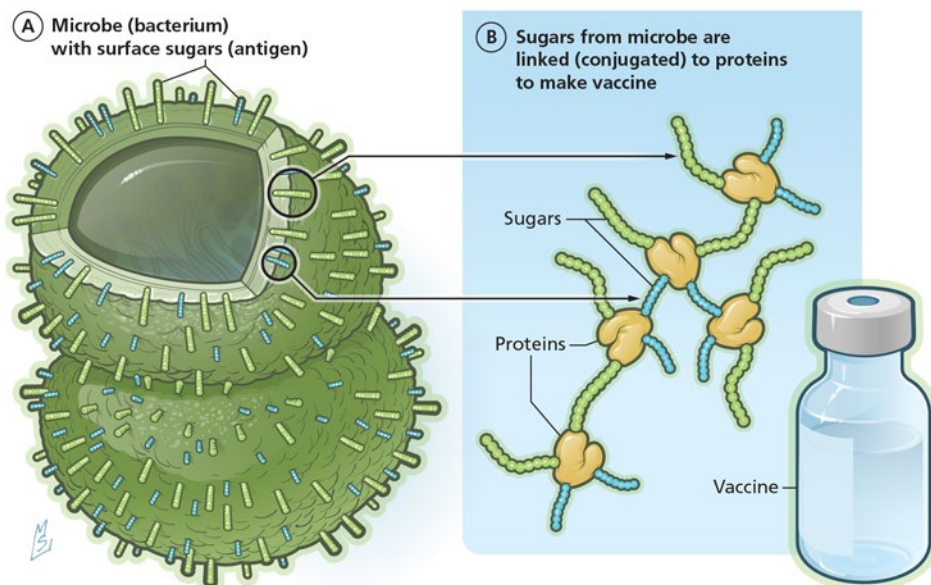
outbreaks are especially prevalent in areas that offer exemptions for parents to enroll their children in public schools without vaccinating them.

This recent trend is disturbing because, as vaccination rates decrease, people with compromised immune systems and infants too young to be vaccinated will succumb to deadly infections spread by the unvaccinated. Vaccines protect not only individuals but entire communities, offering what is known as herd immunity. As an article in *The Economist* noted, "A large vaccinated population forms a fence around those who are susceptible, keeping diseases away. In communities where anti-vaccine sentiment is strongest, the fence is falling down."

A notable example is a recent outbreak of measles traced back to California's Disneyland that spread infection to 17 other states and caused 12 infants too young to be vaccinated to suffer from the disease. A 2013 study found

that between 2004 and 2008 nearly half of US children younger than two years of age received vaccines late or not at all, and these children were 21 percent more likely to be hospitalized than children who were vaccinated on schedule. Due to low vaccination rates, 2014 had the most confirmed cases of measles (644) since 2000 when the CDC declared the illness nearly eliminated in the US.

The problem is that parents are not scared of the disease, according to Paul Offit, a physician at Children's Hospital of Philadelphia who treated children sickened by the disease in a 1991 epidemic brought on by parents who did not vaccinate their children. "These children would come in covered in rashes, struggling to breathe and often extremely dehydrated," he wrote in a recent editorial in *The New York Times*. "It was like being in a war zone."



**Figure 10 – Conjugate vaccine:** Conjugate vaccines combine pieces of the bacteria's sugar coat with a protein carrier to enhance the immune response to the bacteria. *Illustration: © Michael Linkinhoker, Link Studio, LLC.*

B cells to produce antibodies that latch onto the antigens of foreign intruders and mark them for destruction. Helper T cells also foster the production of cytotoxic T cells, which detect and kill infected cells and stimulate the production of “memory” B cells, sentries that stick around after an initial response to respond more quickly to re-infections by the same microbe.

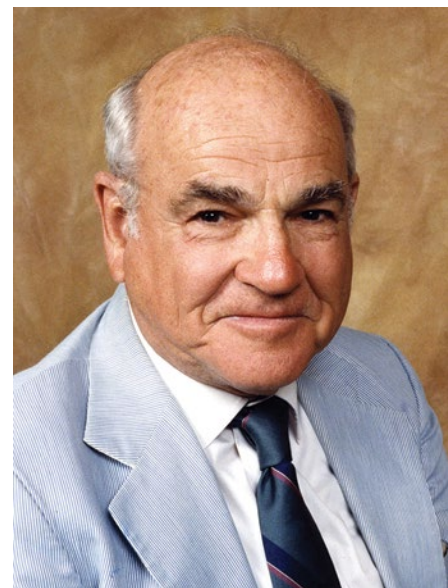
By the 1970s, scientists knew that an effective and long-lasting immune response to a pathogen involved not just producing antibodies but activating T cells as well. Using this basic information, the stymied vaccine makers discovered that the sugar antigens on the outside of bacteria did not stimulate a T cell response but rather directly stimulated B cells. This explained why the meningitis and pneumonia vaccines were only effective for older children and adults—the vaccines made individuals previously infected with the pathogens or similar microbes better able to fight re-infection. But the vaccines did not stimulate T cells, which are needed to mount a quick, effective, and long-lasting immune response

in infants and other young children who have never been exposed to the pathogen.

Fortunately, in the early twentieth century, researchers found that when the sugar component of the pneumonia bacteria was linked (conjugated) to a protein, it triggered greater production of antibodies. Revisiting this finding, John Robbins and colleagues at NIH hypothesized that the added protein elicited the critical immune response from helper T cells. They then linked the sugar antigen from the bacteria that cause meningitis to the protein toxin made by the diphtheria bacteria. This first sugar-protein conjugate vaccine entered the market in 1987 and proved highly effective in preventing meningitis in children as young as two months of age. Similar conjugate vaccines that improved the effectiveness of pneumonia vaccines for small children came on the market about the same time.

## Recombinant vaccines

Another type of vaccine that revolutionized immunizations targeted hepatitis B, a disease that had plagued



**Figure 11 – Baruch Blumberg:** Baruch Blumberg discovered that proteins shed by the hepatitis B virus could be used to make an effective vaccine for the disorder. This led to the first vaccine made without cultivating the microbe that caused it. *Image credit: Fox Chase Cancer Center*

humankind since the beginning of recorded history. Hepatitis B causes acute infection (hepatitis), and in some, can lead to chronic infection, causing fatigue, jaundice, abdominal pain, and liver damage, which can result in liver failure or cancer. Children infected at birth or during infancy are particularly prone to developing chronic hepatitis B infection.

A hepatitis B vaccine got its start in the 1960s when Baruch Blumberg, a specialist in genetics, wondered why people were prone to certain diseases. With support from NIH, he combed through blood samples collected from ethnically diverse people around the world to search for genetic clues that might explain susceptibility to disease. In the process, he accidentally discovered something that later won him the Nobel Prize—people infected with hepatitis B had in their blood large quantities of particles that contain proteins found in the outer coat of the hepatitis B virus.

These particles had no viral DNA so they could not cause infection, but they did stimulate an effective immune response to hepatitis B in people who received blood transfusions contaminated with the virus particles. Blumberg proposed the particles be used in a vaccine against hepatitis B. In 1981, FDA licensed the first vaccine for hepatitis B, which used heat and chemicals to inactivate the virus in the plasma of infected individuals, leaving behind its outer coat proteins that stimulate an immune response.

Subsequently, Maurice Hilleman of Merck genetically engineered yeast to produce the viral proteins and, for the first time, made a vaccine without cultivating the microorganism responsible for the disease! Merck's recombinant vaccine, which came on the market in 1986, is 95 percent effective at preventing hepatitis B and has reduced the rate of chronic infection in children from 15 to less than one percent. The vaccine also prevents liver cancer that can arise from a chronic hepatitis B infection. Because the recombinant hepatitis B vaccine is safer, production of the plasma-derived vaccine was halted in 1990 and is no longer available in the US.

A similar procedure was used to make vaccines for other viruses that cannot be grown in cell culture, including the human papilloma virus (HPV), which can cause cervical cancer. The first HPV vaccines came on the market in 2006 and 2009. A newer vaccine followed in 2015, which protects against more types of HPV, and is expected to reduce the risk of cervical cancer by 90 percent and lower the risk of vaginal, anal, and throat cancers that are also caused by this virus. (See *Breakthroughs in Bioscience* article, "Viruses, Cancer, Warts and All: The HPV Vaccine for Cervical Cancer.")

Despite all the progress made in the twentieth century, researchers still were not able to elicit sufficient



**Figure 12 – Beutler, Hoffmann, Steinman:** Bruce Beutler, Jules Hoffmann, and Ralph Steinman received the 2011 Nobel Prize in Physiology or Medicine for their discoveries of the cells and receptors that play a critical role in the immune system's first line of defense. Their discoveries prompted the creation of safer and more effective vaccines. Image credits: © HO/Reuters/Corbis (Beutler), Holger Motzkau (Hoffmann), The Rockefeller University (Steinman)

immune responses with vaccines for other killer diseases, including the ancient scourge malaria. For over a century, scientists had been unsuccessful at producing an effective vaccine for this disease, which kills more than one million people a year—mostly children under the age of five—and causes repeated debilitating bouts of illness in those that survive. A new battle strategy was needed and, once again, basic findings in immunology led the charge.

## Taking its Toll



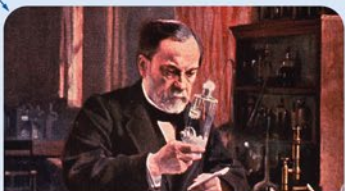
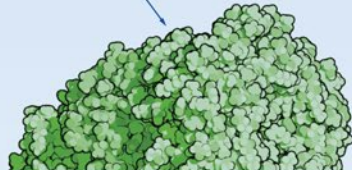
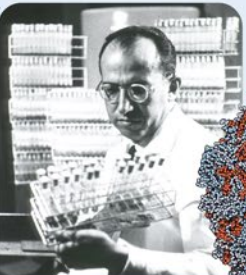
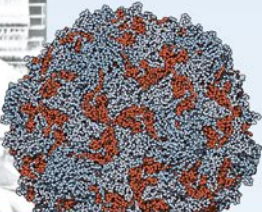
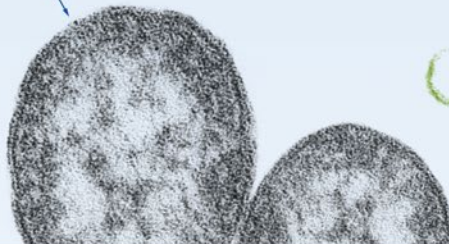
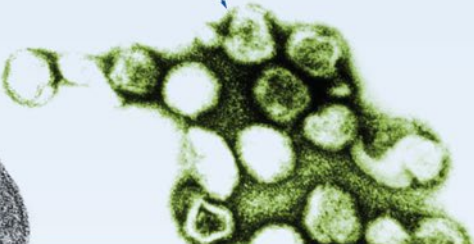
In the 1990s, biologist Jules Hoffmann of the University of Strasbourg was puzzling over how animals that lacked T and B cells, such as insects or the starfish larvae that Metchnikoff experimented on, protected themselves from infection. With support from France's National Center for Scientific Research, Hoffmann did research on fruit flies that had a defective gene called *Toll*. These flies fell victim to fungal infections unlike normal flies. Hoffmann discovered the *Toll* gene codes for a specific cell surface receptor that can detect certain features in microbes and send out biochemical signals that prompt an immune response against the invaders. Hoffmann's discovery revealed the genetic basis of the physiological response to bacteria, which had

been studied for over 100 years. Other groups went on to further elucidate this response in humans and other mammals

Bruce Beutler at the University of Texas Southwestern Medical Center was trying to understand how bacterial sugar-fat complexes trigger an extreme immune response called septic shock (blood poisoning). The body's immune defense must have a specific receptor that is activated by these foreign sugar-fat complexes, Beutler reasoned. With support from NIH and the Howard Hughes Medical Institute, he searched systematically through mouse mutants that lacked the ability to react to these sugar-fat complexes and discovered they had a mutation in a gene similar to the fruit fly's *Toll*. This mouse gene coded for what is called a Toll-like receptor (TLR), which in normal mice triggers septic shock when activated.

During the 1980s and 1990s, immunologist Ralph Steinman at Rockefeller University discovered in mice a new cell with branch-like extensions he called a dendritic cell. With support from NIH, Steinman and other scientists showed that when components of bacteria, viruses, or other pathogens are detected by the TLRs of dendritic cells, the cells mature, devour the intruders, and travel to the lymph nodes. There, they

## VACCINES TIMELINE

<p><b>1796</b> <b>SMALLPOX</b></p> <p>Edward Jenner inoculated a small boy with pus from a cowpox blister</p> 	<p><b>1800</b> <b>SMALLPOX</b></p> <p>Demonstrated efficacy of Jenner's vaccine resulted in widespread use</p> 	<p><b>1885</b> <b>RABIES</b></p> <p>Louis Pasteur inoculated a boy with a weakened rabies virus</p> 	<p><b>1896</b> <b>CHOLERA</b></p> <p>A vaccine against cholera was developed using the heat-inactivated bacteria, <i>Vibrio cholerae</i></p>	<p><b>1896</b> <b>TYPHOID</b></p> <p>Vaccination with weakened typhoid bacteria resulted in protection against typhoid fever</p> 
<p><b>1955</b> <b>POLIO</b></p> <p>Jonas Salk produced the first successful polio vaccine</p> 	<p><b>1960</b> <b>POLIO</b></p> <p>Albert Sabin developed a more effective oral form of the polio vaccine</p> 	<p><b>1963</b> <b>MEASLES</b></p> <p>Testing in monkeys and humans showed safety and efficacy of the measles vaccine</p> 	<p><b>1967</b> <b>MUMPS</b></p> <p>Using virus isolated from his daughter, Maurice Hilleman developed the vaccine that protects against mumps</p>	<p><b>1969</b> <b>RUBELLA</b></p> <p>The rubella vaccine was licensed in 1969 after the virus was first isolated in 1962</p> 

*Image credits: Centers for Disease Control (Smallpox virus/vaccine, Tuberculosis culture, Diphtheria toxin, Pneumococcal culture, Polio virus, Measles virus, Rubella virus, Hepatitis B virus, and Human Papilloma virus), National Library of Medicine (Pasteur, Salk, and Hilleman), ThinkStock (Typhoid toxin), Michigan Women's Historical Center & Hall of Fame (Kendrick and Eldering), Wikimedia Commons/Creative Commons (Human Papilloma vaccine); Design: Michael Linkinhoker, Link Studio, LLC.*

display the intruders' antigens like red flags to circulating T cells, which start to multiply, mature, and seek out the microbial antigens to trigger a full-fledged immune response.

The discovery of TLRs and dendritic cells resolved the debate about which arms of the immune system—innate or adaptive—were most critical for mammalian immune defenses. They both were! Much weight had been given to antibodies, but the first responders to infection—the phagocytes Metchnikoff observed and dendritic cells—played a key role in triggering later T and B cell responses and antibody production. In 2011, Beutler, Hoffmann, and Steinman won the Nobel Prize in Physiology or Medicine for their discoveries that

furthered the development of more effective vaccines.

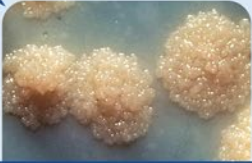


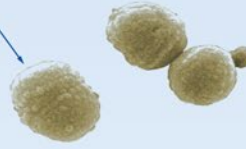
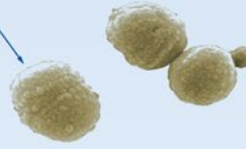

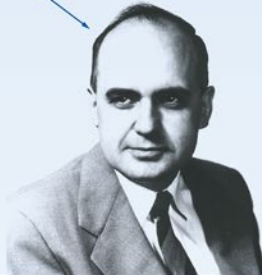
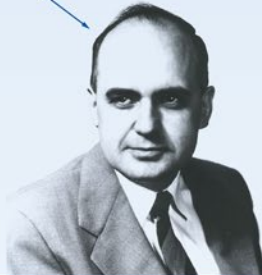

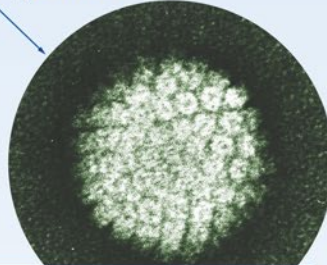
Ten TLRs have been discovered in people. These receptors are not as specific as those on T and B cells, which can zero in with exquisite precision on the antigens under attack. Instead, TLRs recognize molecular patterns broadly shared by pathogens, such as bacterial or viral sugars, proteins, and nucleic acids. By adding these compounds or their mimics to vaccine antigens, investigators have been able to create more effective vaccines.

### The future of vaccines

Vaccination has been remarkably successful over the past two centuries. According to the Centers for Disease

Control and Prevention (CDC), there are now 27 diseases that are vaccine-preventable, including close to a dozen childhood diseases whose incidence have dramatically decreased compared to when vaccines were unavailable. Each year in the US, vaccines are estimated to save the lives of 36,000 people, most of whom are children. Largely because of vaccines, instead of dying in infancy, most babies born today will live long and productive lives.

Using advances in genetics and immunology, investigators continue to develop new kinds of vaccines that hold promise for better efficacy by eliciting immune responses similar to those that occur naturally upon entry of an intruding microbe. Some

<p><b>1921</b> <b>TUBERCULOSIS</b></p> <p>A weakened form of the tuberculosis bacterium, <i>Mycobacterium tuberculosis</i>, was used to develop an oral tuberculosis vaccine</p> 	<p><b>1923</b> <b>DIPHTHERIA</b></p> <p>Scientists in France and England developed vaccines against diphtheria using deactivated diphtheria toxins</p> 	<p><b>1924</b> <b>TETANUS</b></p> <p>A vaccine composed of deactivated tetanus toxin proved effective against tetanus</p> 	<p><b>1939</b> <b>PERTUSSIS</b></p> <p>Pearl Kendrick (l) and Grace Eldering (r) created one of the first vaccines for pertussis (whooping cough)</p> 	<p><b>1946</b> <b>PNEUMOCOCCAL VACCINE</b></p> <p>FDA approved the first subunit vaccine developed from the sugar molecules on pneumococcal bacteria</p> 
<p><b>1986</b> <b>HEPATITIS B</b></p> <p>FDA licensed the recombinant hepatitis B vaccine, which was developed using genetically modified yeast</p> 	<p><b>1987</b> <b>HAEMOPHILUS INFLUENZAE TYPE B</b></p> <p>John Robbins and colleagues at NIH developed the first conjugate vaccine against meningitis</p> 	<p><b>1995</b> <b>CHICKENPOX</b></p> <p>Maurice Hilleman developed the first vaccine to protect against chickenpox</p> 	<p><b>2006</b> <b>HUMAN PAPILLOMA VIRUS</b></p> <p>FDA licensed a vaccine to protect against human papilloma virus (HPV) types 6, 11, 16, and 18, viruses, which can cause cervical cancer</p> 	<p><b>2015</b> <b>HUMAN PAPILLOMA VIRUS</b></p> <p>FDA approved a new vaccine that protects against nine types of HPV</p> 

vaccines can be delivered into the skin with a microneedle, rather than via the traditional shot into a muscle. The expectation is that these intradermal vaccines will be more effective because they will encounter more immune response-stimulating dendritic cells in the skin. Other vaccines build on advances in genetic and protein screening of microbes that have led to the identification of new antigens. Such techniques have been applied to make experimental vaccines offering protection against staph, strep, and pathogenic *E. coli* infections.

A new approach to making vaccines is to insert key antigens into the genetic material of weakened viruses. These viruses cannot cause disease yet are still able to infect cells, which respond to the antigens they carry the same way they would respond to a natural infection. Because of how well they mimic natural protection from infection, vaccines created in

this manner are expected to offer longer lasting protection. Researchers are currently evaluating this type of recombinant vaccine for HIV, rabies, and measles, among other diseases.

Some research groups are also investigating DNA vaccines, which consist of just a small number of genes that code for a pathogen's antigens. When these genes are injected into the skin, some cells take up the DNA, begin making the encoded antigen molecules, and display it on their own surfaces. Because these antigens stimulate the production of antibodies as well as the expansion of dendritic, helper, and cytotoxic T cells, they activate both innate and adaptive immunity. The next time the immune system encounters the same antigens, it destroys the pathogen before it has a chance to cause disease. The DNA vaccine contains such a small number of microbial genes that it cannot cause disease itself. While this work

is promising, there are obstacles that must be overcome in order to move them into clinical practice. Researchers are currently studying DNA vaccines for influenza, HIV, and herpes.

Scientists have come a long way since Jenner's first inoculation for smallpox. The remarkable progress in fighting infectious diseases was started by scientists who had only their powers of observation. It then blossomed with the insights gleaned by curious scientists over the past century pursuing answers to such basic questions as what causes disease and how do organisms naturally protect themselves from pathogenic microbes. Exploration of these questions by zoologists, chemists, molecular biologists, geneticists, and immunologists revealed ways to harness nature's immune defenses and improve them, resulting in a revolution in the prevention of disease through vaccination. ●

## ADDITIONAL SUGGESTED READING

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Gordon S. "Elie Metchnikoff: Father of natural immunity." *European Journal of Immunology*. 38:3257-3264, 2008.

*mLIVE* January 25, 2015 "How 2 women scientists, helped by Grand Rapids, created whooping cough vaccine" by Sue Thoms ([http://www.mlive.com/news/grand-rapids/index.ssf/2015/01/how\\_grand\\_rapids\\_led\\_by\\_two\\_wo.html](http://www.mlive.com/news/grand-rapids/index.ssf/2015/01/how_grand_rapids_led_by_two_wo.html))

*Los Angeles Times* April 10, 2005 "The Unsung Women in the Race for the Polio Vaccine" by David M. Oshinsky (<http://articles.latimes.com/2005/apr/10/opinion/oe-oshinsky10>)

*The New York Times* May 6, 2013 "A Forgotten Pioneer of Vaccines" by Richard Conniff (<http://www.nytimes.com/2013/05/07/health/maurice-hilleman-mmr-vaccines-forgotten-hero.html>)

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The History of Vaccines (<http://www.historyofvaccines.org/>)

Finco O. and Rappouli R. "Designing Vaccines for the Twenty-First Century Society." *Frontiers in Immunology*. 5:12, 2014.

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## BIOGRAPHIES

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**Margie Patlak** writes about biomedical research and health from the Philadelphia region. She has written for *Discover*, *Glamour*, *Physician's Weekly*, *Consumer Reports on Health*, *The Washington Post*, *Los Angeles Times*, *Dallas Morning News*, and numerous other publications. She frequently writes for the National Institutes of Health and the National Academy of Sciences and currently works with a number of trade journals, such as *Endocrine News* and the *Journal of the National Cancer Institute*. This is her tenth article in the *Breakthroughs in Bioscience* series.

**Nilabh Shastri, PhD** is a Professor of Immunology and Pathogenesis at the University of California Berkeley. He researches mechanisms of immune surveillance, specifically of intracellular pathogens. With support from the National Institutes of Health (NIH), he has developed novel methods to identify T cell activating peptide antigens in tissue transplants, microbes, parasites, and cancer cells. In addition, his group has made seminal discoveries in understanding antigen producing pathways. He serves on the Editorial Boards of the *Journal of Experimental Medicine* and *Frontiers in Immunology* and on many review panels at NIH. Dr. Shastri earned his PhD in biochemistry at the All India Institute of Medical Sciences and received postdoctoral training in cellular and molecular immunology at the University of California Los Angeles and Caltech.

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